> In Autogiro Co. of America v. United States, 384 F.2d 391, 397, 155 USPQ 697, 702 (Ct. Cl. 1967), our predecessor court recognized that patentees are not confined to normal dictionary meanings:
>
> > The dictionary does not always keep abreast of the inventor. It cannot. Things are not made for the sake of words but words for things. To overcome this lag, patent law allows the inventor to be his own lexicographer. (Citations omitted.)
>
> A patentee's verbal license "augments the difficulty of understanding the claims," and to understand their meaning, they must be construed "in connection with the other parts of the patent instrument and with the circumstances surrounding the inception of the patent application." Id. Accord, General Electric Co. v. United States, 572 F.2d 745, 751-53, 198 USPQ 65, 70-73

Accordingly, the term "nuclear export protein" should be read consistent with the definition provided in the specification. Therefore, a nuclear export sequence directs the export of a polypeptides from the nucleus and/or maintains the "exported" status of the fusion protein; once the repressor polypeptide containing a nuclear export sequence is cleaved from the reporter polypeptide, the reporter polypeptide is released from its localization outside the nucleus. Thus, when a fusion protein contains a repressor protein comprising a nuclear export sequence according to claim 3, the fusion protein is localized to a region other than the nucleus. Cleavage of the fusion protein linker at a protease cleavage site results in localization of the reporter polypeptide, such as a transcription factor, in the nucleus.

However, in order to expedite prosecution of the application, claim 3 has been amended consistent with the above-cited language from the specification. Therefore, Applicants submit that the meaning of claim 3 and claims dependent therefrom are not indefinite. Accordingly, reconsideration and withdrawal of the rejection under 35 U.S.C. § 112, second paragraph is respectfully requested.

The rejection of claims 3 and claims 4 to 7, dependent therefrom, under 35 U.S.C. § 112, first paragraph, as allegedly lacking enablement is respectfully rejected.

Applicants respectfully disagree with the Examiner's assertion that one of skill in the art would consider such a protein sequence to direct the localization of said protein from inside the nucleus to outside the nucleus. As discussed previously, the definition of "nuclear export sequence" provided in the specification is a polypeptide that directs the polypeptide to a region of a cell outside of the nucleus. The specification provides numerous sequences according to the definition. For example, CD4 transports a polypeptide outside of the nucleus (Specification, page 14, lines13 to14). Further exemplary localization sequences provided include sequences targeting mitochondria, *e.g.*, SEQ ID NO:3, sequences targeting endoplasmic reticulum, sequences targeting plasma membrane and sequences targeting the Golgi apparatus (see Specification, page 14, line 25 to page 15, line 4).

Applicants respectfully submit, in contrast to the Examiner's assertion, that the specification need not describe a polypeptide that directs the localization of the polypeptide from inside the nucleus to outside the nucleus. The specification provides descriptions of polypeptides that direct the localization of proteins to regions of a cell outside the nucleus according to the definition provided in the specification of the term "nuclear export protein". Moreover, in view of the amendment of claim 3 to incorporate language from the specification and recited repressor polypeptide comprising a polypeptide sequence that directs the polypeptide to a region of a cell outside the nucleus, claim 3 and claims dependent therefrom are fully enabled.

Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejection under 35 U.S.C. § 112, first paragraph.

Claim Rejections Under U.S.C. § 102

The rejection of claims 1, 2, 3 and 9 under 35 U.S.C. § 102(e) as allegedly being anticipated by Tsien *et al.* (U.S. Patent Number 5, 981,200, hereinafter "Tsien") is respectfully traversed.

Applicants invention, as defined in claim 1 and claims 2 and 3, dependent therefrom (claim 9 having been canceled), distinguishes over the art by requiring a fusion protein comprising a reporter polypeptide linked to a linker polypeptide and a repressor polypeptide that represses the activity of the reporter polypeptide. Upon cleavage of the linker polypeptide at a protease cleavage site, activity of the reporter polypeptide is increased. Repressor polypeptides include an N-terminal fragment of CD4 and amyloid precursor protein. Reporter polypeptides include transcription factors such as C-terminal Lex A-B42 and kinases.

In contrast, Tsien teaches a tandem fluorescent protein construct comprising a donor fluorescent protein moiety, an acceptor fluorescent protein moiety, and a peptide linker that couples the donor and acceptor fluorescent protein moieties. Upon excitation of the donor moiety, fluorescence resonance energy is transferred to the acceptor moiety. Tsien teaches only fluorescent protein moiety constructs that transfer fluorescence resonance energy. Tsien does not teach or suggest a using protein constructs containing a repressor protein and a reporter protein. Indeed, Tsien does not teach or suggest using any protein moiety other than fluorescent protein moieties. Therefore, Tsien does not anticipate Applicants' invention.

Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejection under 35 U.S.C. § 102.

The rejection of claims 1, 3 and 9 under 35 U.S.C. § 102(b) as allegedly anticipated by Knight *et al.* (*Methods in Enzymology*, (1995) 248:18-34; hereinafter "Knight") is respectfully traversed.

Applicants invention, as defined in claim 1, distinguishes over Knight by requiring a fusion protein comprising a reporter polypeptide linked to a linker polypeptide and a repressor polypeptide that represses the activity of the reporter polypeptide. Upon cleavage of the linker polypeptide at a protease cleavage site, activity of the reporter polypeptide is increased. In contrast, Knight teaches constructs of fluorescent proteins including a peptide linker. As acknowledged by the Examiner, Knight teaches constructs that employ resonance energy transfer. Knight does not teach or suggest using non-fluorescent protein moiety constructs. Therefore, Knight does not anticipate Applicants' invention.

Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejection under 35 U.S.C. § 102(b).

In view of the above amendments and remarks, reconsideration and favorable action on all pending claims are respectfully requested. In the event any matters remain to be resolved in view of this communication, the Examiner is requested to telephone Applicants' representative, Lisa A. Haile, J.D., Ph.D., at (858) 677-1456 or the undersigned so that a prompt disposition of this application can be achieved.

Respectfully submitted,

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EXHIBIT A: CLAIMS AS THEY WILL STAND UPON ENTRY OF AMENDMENTS

1. A fusion protein comprising:

   (a) a reporter polypeptide linked to a linker polypeptide comprising a protease cleavage site; and

   (b) a repressor polypeptide that represses the activity of said reporter polypeptide, wherein said repressor polypeptide is operatively linked to the linker polypeptide, and

   wherein cleavage of said linker polypeptide at said protease cleavage site increases the activity of said reporter.

2. The fusion protein of claim 1, wherein said protease cleavage site is a caspase cleavage site.

3. (Amended) The fusion protein of claim 1, wherein said repressor polypeptide comprises a polypeptide sequence that directs the localization of said fusion protein outside of the nucleus of a cell.

4. The fusion protein of claim 3, wherein said repressor polypeptide is an N-terminal fragment of CD4.

5. The fusion protein of claim 3, wherein said reporter polypeptide is a transcription factor.

6. The fusion protein of claim 5, wherein said transcription factor is C-terminal Lex A-B42 transcription factor.

7. The fusion protein of claim 3, wherein said repressor polypeptide is amyloid precursor protein.

8. The fusion protein of claim 1, wherein said reporter polypeptide is a kinase.